
CIRM Cancer Stem Cell Workshop Summary

CIRM WORKSHOP SUMMARY: CANCER STEM CELLS

8/26/08, Luxe Hotel, Los Angeles

Participants:

Karen Aboody, City of Hope
Ted Ball, UCSD
David Baltimore, Caltech
Ravi Bhatia, City of Hope
Dennis Carson, UCSD
Mike Clarke, Stanford
Brian Henderson, USC
Catriona Jamieson, UCSD
Irv Weissman, Stanford
Owen Witte, UCLA

Alan Trounson, CIRM
Marie Csete, CIRM
Patricia Olson, CIRM
Michael Yaffe, CIRM
Don Gibbons, CIRM

The workshop was charged with the goals of discussing CIRM's involvement in cancer stem cell (CSC) research and exploring how cooperative programs between CIRM and Genome Canada/Canadian Consortium could catalyze more rapid progress in the this important field. Dr. Alan Trounson pointed out that CIRM's mission to facilitate biomedical research progress encompasses research beyond human embryonic stem cells (hESCs) and may include studies with adult stem cells, induced pluripotent stem cells (iPSC), as well as small molecule discovery. Research on cancer already comprises approximately 10% of CIRM's research grant portfolio.

Throughout the meeting, there were recurrent discussions about the possibilities for collaboration on CIRM-funded projects. Participants acknowledged the leadership of Canada in CSC research and the value of collaboration between CA and Canadian scientists while at the same time emphasizing the importance of

collaboration as being between scientists and not mandated by government entities. It was emphasized that CIRM funds are restricted to support of research within California. The distinct feature of a CIRM-sponsored joint collaborative effort (e.g. with Genome Canada/Canadian Consortium) would be the possibility of initiating a research project with both California and collaborative components reviewed and funded simultaneously. Synergistic collaborations could enhance the proposal's standing in the review process by ensuring more comprehensive project coordination and the immediate availability of appropriate resources. Several participants stressed the desirability of fostering other types of out-of-state collaborations on CIRM-funded projects; although no mechanism currently exists to include such arrangements, CIRM may develop policies in the future to facilitate collaborations with other externally funded partners.

Dr. Irv Weissman (Stanford) discussed the development and state of the CSC field. He described the identification of a rare cell population among leukemic cells that were shown by transplantation into immune-compromised mice to be self-renewing and sufficient for repeated serial transplantation, giving rise to the full heterogeneous cell composition of the original tumor. Some data indicate that these tumor-initiating CSC's are more resistant to cancer chemotherapeutic drugs than the bulk tumor cells and contribute to the recurrence of cancers after chemotherapy. CSC's for blood cancers are likely to arise by mutation of either hematopoietic stem cells (HSCs) or partially differentiated, multipotent cells in the hematopoietic lineages.

Weissman emphasized the adaptation and evolution of cancer cells during disease progression and in culture (in vitro), and he suggested that these processes are likely to yield cells with different properties. Consequently, drugs developed using cancer cell lines may show reduced effectiveness on cancer cells in situ. In illustrating important molecular differences between leukemic CSC's and normal cells in the hematopoietic lineages, Weissman presented data on CD47, a cell surface marker expressed at high levels on leukemic cells. CD47 binds to the SIRP-alpha receptor on macrophages and blocks phagocytosis. Such a block may contribute to the evasion of immune defenses by cancer cells, and treatment of leukemic cells with anti-CD47 prevents their growth in a model system.

Weissman highlighted barriers to progress in CSC research. These include insufficient access by researchers to tumor samples collected and stored to maintain cell viability, development of better immunodeficient mice and provision of core resources for immunodeficient mice, lack of availability of multi-parameter highspeed cell sorters, and lack of adequate core translational infrastructure (QA/QC, regulatory etc). Moreover, he maintained that NIH funding for CSC research is inadequate.

Dr. Owen Witte (UCLA) identified roadblocks and critical, rate-limiting issues in CSC research that have emerged from discussion with Canadian researchers. These include problems with acquisition of biopsy, surgical, and autopsy materials, inadequacy of technical resources (e.g. core resources for GMP and immunodeficient mice), lack of critical mass of researchers, and inadequate attention to cancers typical of specific human populations. He further emphasized the need for RFA's addressing different stages of cancer research (e.g. discovery, translation) and suggested grants of varying size depending on scope and focus.

Catriona Jamieson (UCSD) presented research from her lab on myeloproliferative disorders (MPD) and the clonal involvement of hematopoietic pluripotent cells in these diseases. She described an activating mutation in the JAK2 tyrosine kinase common to MPDs and reported studies and an ongoing clinical trial with the kinase inhibitor, TG101348, in patients with myelofibrosis. She emphasized a crucial need for further research on CSC's to identify therapeutic targets and develop strategies to block abnormal differentiation and interfere with CSC self-renewal, survival, and homing. Jamieson also cited several advantages of collaborations with Canadian scientists including the complete reciprocity of training systems between the US and Canada, cultural similarities of the two countries, and extensive networks for clinical trials that are already established.

Mike Clarke (Stanford) described studies that illuminate mechanisms by which multipotent progenitor cells can acquire the ability to self-renew. This is thought to be a key step in the generation of those CSC's which are not derived from adult stem cells. Mutation of genes such as Bmi-1, p53, p19, and p16, led to acquisition of self-renewal by common myeloid progenitor (CMP) cells, suggesting that these genes normally play a role in limiting the expansion of multipotent progenitors. Clarke also reported that self-renewal associated genes are over-expressed in breast CSC's and in a subset of epithelial CSC's. These studies illustrate the importance of comparative analysis of normal tissue, CSC's, and bulk tumor cells and the need for further basic research on CSC's. Additionally, Clarke suggested that further research on CSC's should be motivated by concerns over the oncogenic potential of cell transplantation; he cited a recent study of transplantation of human pancreatic endoderm in which 15% of the recipient mice developed oncogenic tumors.

Participants identified a number of scientific or technical obstacles impeding more rapid progress in CSC research. Foremost among these is the need to identify and characterize the detailed developmental pathways leading to the terminally differentiated cell types found in mature tissues. The availability of such information was essential for identification and analysis of leukemic CSCs in the hematopoietic pathway. A related challenge to the field is the need to identify and characterize CSCs for the vast majority of cancer types (note: there is no consensus in the cancer field that most or all neoplasms are driven by CSCs). Additional roadblocks include a deficiency of appropriate biomarkers to identify and purify specific cell types, inadequate animal models, and the need to develop relevant cell-based assays for small molecule screening.

Several participants were unconvinced that there were compelling reasons for specific collaborations with Canadian researchers. They expressed concerns that such associations were (or would be) artificially imposed, rather than synergistic and natural outgrowths of common research interests. A further concern was that international collaborations would likely be burdened by added legal and logistical complications.

Others pointed out that Canada is a willing and able partner in CSC research. Canada and California are already centers for CSC research, with Canadian scientists desiring to partner their strength in cancer research with California expertise in stem cell biology. Some fruitful collaborations in this area already exist. Genome Canada has experience in large-scale collaborations and consortium development and has expressed a willingness to participate in joint programs with CIRM. Additionally, a successful cooperative program could serve as a model for future national or international collaborative efforts.

One suggested role for CIRM funding and/or Canadian collaboration is in the development of essential infrastructure for research support and therapeutic development. A primary need is for a tumor or tissue bank (and/or a coordinated tissue distribution network) which would make patient samples readily available for research. A second needed resource is a facility for production and maintenance of appropriate animal models, particularly immune-deficient or humanized mice. Additional infrastructure needs include facilities for large-scale genomic analysis, centers for advanced imaging technology and microfluidic-bioengineering technical development, and production facilities for monoclonal antibodies.

There appeared to be unanimous support and agreement on three key points:

1. CIRM should expand its support of CSC research both via inclusion of CSC research in broader RFAs (e.g. Disease Teams) and through specifically targeted RFAs.
2. CIRM should encourage and facilitate research collaborations (within the constraints of CIRM policies) when these arrangements will enhance research progress and enable CIRM's mission.
3. The CIRM-Genome Canada/Canadian Consortium collaboration is a promising opportunity that should be pursued and developed.